

CORRES. AND MAIL  
**BOX AF**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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#26  
49.96  
R.P.

In re application of :

Heribert SCHMITT-WILLICH et al. :

Serial No.: 08/319,357 :

Filed: October 6, 1994 :

BOX AF

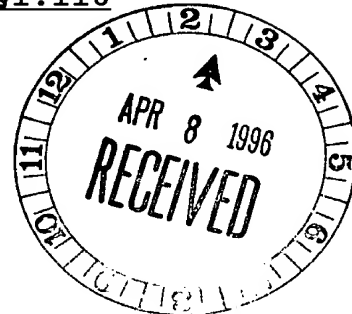
Group Art Unit: 1208

Examiner: L. Chapman

For: DERIVATIZED DTPA COMPLEXES, PHARMACEUTICAL AGENTS CONTAINING THESE COMPOUNDS, THEIR USE, AND PROCESSES FOR THEIR PRODUCTION

REQUEST FOR RECONSIDERATION UNDER 37 C.F.R. §1.116

Assistant Commissioner for Patents  
Washington, D.C. 20231



SIR:

In response to the Office Action of November 30, 1995, applicants hereby respectfully request reconsideration of the rejection under 35 U.S.C. §103.

In the rejection, it is asserted that it would be obvious to modify the chelate complexes disclosed by Berg et al. (EP '795 or U.S. '208) by substitution of a benzyl structure for the alkyl portion of a pendant group in light of the disclosure of Gries et al. (EP '059). Applicants do not agree as discussed at pages 4-9 of the Amendment filed September 1, 1995.

To further emphasize the nonobvious character of applicants' invention, enclosed herewith is a Rule 132 Declaration to be executed by Dr. Gabriele Schuhmann-Giampieri, one of the inventors. The enclosed copy of the Rule 132 Declaration is presently unexecuted. An executed version will be submitted in the near future.

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In the Rule 132 Declaration, comparative test results are presented for the compounds Gd-ethoxybenzyl DTPA (elected species), Gd-methoxybenzyl DTPA and Gd-methoxymethyl DTPA. As can be seen, the difference between the second and third compounds is that the second compound exhibits a benzyl structure in place of a methyl structure present in the third compound.

In the first set of tests, excretion and relaxivity data were determined for Gd-methoxybenzyl DTPA and Gd-ethoxybenzyl DTPA. Both chelate complexes exhibited significant biliary excretion in the time period of up to 4 hours after administration. The methoxybenzyl compound exhibited a biliary excretion of 44.6%. The biliary excretion of the ethoxybenzyl compound was even higher, i.e., 73.9%. As regards to  $T_1$  relaxivity, the ethoxybenzyl chelate complex exhibited higher relaxivity values in both water (5.33 l/mmol·sec versus 4.54 l/mmol·sec) and plasma (8.69 l/mmol·sec versus 6.89 l/mmol·sec).

In the second experiment, excretion values were obtained for the methoxymethyl compound in comparison with the ethoxybenzyl compound. In terms of biliary excretion, the methoxymethyl compound within a time period of 4 hours after administration was barely excreted at all, i.e., an amount of less than 1%. The urinary excretion was significantly higher, i.e., 75.6%. On the other hand, the ethoxybenzyl compound exhibited a significantly higher biliary excretion within the first 4 hours after administration, i.e., more than 68%.

Taking all of the test data together, it is evident that the ethoxybenzyl and methoxybenzyl compounds exhibit substantially higher biliary excretion than the methoxymethyl compound. For ethoxybenzyl, the biliary excretion was 73.9% in one set of experiments and 68.2% in another set of experiments. The methoxybenzyl compound had a biliary excretion of 44.6%. Conversely, the methoxymethyl compound had a biliary excretion of less than 1%.

Thus, the compounds having a benzyl structure show a significantly higher biliary excretion in comparison to the compound exhibiting an alkyl structure. As a result, contrary to the assertion in the rejection, substitution of a benzyl structure

for the alkyl portion of a pendant group clearly results in a nonobvious modification.

In view of the above remarks, reconsideration of the rejection under 35 U.S.C. §103 is respectfully requested.

**Election**

Applicants hereby confirm election of the compound of Example 8c. With respect to the claims withdrawn from consideration, applicants assume that, upon indication of allowability with respect to a generic claim, these claims will be brought back into prosecution. Moreover, it does not appear that examination of the claims withdrawn from consideration with the examined claims imposes any undue burden. Up until the final rejection, all claims were being examined together.

Respectfully submitted,



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